

REMARKS

Claims 1 to 6, 10 to 18, and 22 to 27 as amended and new Claims 28 to 31 are present.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claims 1, 15 and 22, the only independent claims present, have been amended to define both the lithiating step (a), and the coupling step (b) (where the lithiated anion species is coupled with a carbonyl substituted reactant to form a glycoside) as being carried out (in a continuous process) at non-cryogenic temperatures. In essence, Applicants are combining Claims 1 and 8, Claims 15 and 1, and Claims 22 and 24.

New Claims 28 to 31 define the PG protecting group based on the disclosure at page 17, lines 8 to 10 of the specification.

As will be seen, the cited Czernecki et al. reference discloses a batch process where the lithiating step (a) is carried out at non-cryogenic temperatures and the coupling step (b) is carried out at cryogenic temperatures with a poor yield of 62% (not 98%). The 98% yield referred to in Czernecki is obtained when removing the protecting groups from the already formed glycoside.

Claim Rejections - 35 U.S.C. §102

Claims 1, 5, 7, 8, 14, 15, 20, 21 and 22 are rejected under 35 U.S.C. §102(b) as being anticipated by Czernecki et al. (J. Org. Chem. 1991, 56:6289-6292).

The Examiner contends that:

“Czernecki et al. teach the reaction of a carbonyl-substituted compound (1) with the lithiated aromatic compound (3a or 3b) to form the glycoside 5 and 8 (see scheme II, page 6290). The lithiated aromatic anionic species is prepared by reacting the aromatic compound 2a or 2b (aromatic halide) wherein bromine (a halide) is the leaving group (Scheme I, page 6289, bottom right). This teaching meets the limitations of claims 1, 5, 8, 15, 21 and 22. The glycoside 8a is hydrogenated to remove the benzyl protecting group to give the glycoside 9a in 98% yield (Scheme II, page 6290; page 6291, right column, see second full paragraph - Preparation of compound 9a). This meets the limitations of claim 7, 14 and 20.”

Applicants' method of making glycosides as now claimed is a non-cryogenic continuous process essentially involving 2 steps, namely lithiating step (a) and coupling step (b), both steps (a) and (b) being carried out at non-cryogenic temperatures.

It is submitted that Applicants' method as claimed is not anticipated by and is patentable over the cited Czernecki et al. reference.

The Examiner maintains that Czernecki teaches the reaction of a carbonyl-substituted compound (1) with the lithiated aromatic compound (3a or 3b) to form the glycoside 5 and 8; and that the lithiated aromatic anion species is prepared by reacting the aromatic compound 2a or 2b (aromatic halide) wherein bromine (a halide) is the leaving group; and that based on such an interpretation of the reference, Claims 1, 5, 8, 15, 21 and 22 are anticipated. Applicants respectfully traverse.

The first step in the Czernecki et al. batch process is a lithiating step carried out at non-cryogenic temperatures, and the second step is the coupling step carried out at -78°C that is at cryogenic temperatures.

The first step in Applicants' continuous process as claimed is a lithiating step carried out at non-cryogenic temperatures and the second step is the coupling step carried out at non-cryogenic temperatures.

Czernecki teaches a batch process for preparation of glycosides and not a continuous process as claimed herein. Czernecki teaches that the debenzylation of the isolated glycoside that produced a 98% yield. The overall yield upon execution of the two steps in the process, lithiation and coupling (prior to the debenzylation) is 62%, not 98%.

In the continuous process of the invention, wherein the first step of forming the lithiated anion is carried out in a microreactor under non-cryogenic temperature, and the second step produces significantly higher yields (than Czernecki et al.) after formation of the lithiated anion, coupling and debenzylation are complete. Performing the first and the second steps of Applicants' continuous process in a microreactor at non-cryogenic temperatures are safer and less expensive than using cryogenic temperatures and improves selectivity in the formation of the lithiated anion and glycoside species. See Specification, pages 3 and 4, and page 12, lines 16-23. Accordingly, yields of up to about 84% (therefore having a correspondingly lower amount of impurities) have been obtained. See Table 1 below which shows that comparative evaluation of the batch process described in Czernecki produced yields of 32% and 40% at non-cryogenic temperatures, and only showed elevated yield (83.6%) when both lithiation and coupling are performed at cryogenic temperatures

(-78°C), whereas the continuous process of the invention produced yields of 76.3%, 72.1% and 70.4% at non-cryogenic temperatures.

Table 1: Preparation of Glycoside

Process	Ex.	Scale (g)	Conditions		Isolated Yield
			Lithiation (solvent, temperature)	Coupling (solvent, temperature)	
Batch processes as run in the standard lab glassware	1	3.0	THF/heptane, -10°C	THF/heptane, -10°C	40.3%
	2	3.0	THF/heptane, 20°C	THF/heptane, 20°C	32.2%
	3	3.0	THF/heptane, -78°C	THF/heptane, -78°C	83.6%
Continuous processes run using a microreactor system (two non-cryogenic steps)	4	4.0	THF/heptane, 20°C	THF/heptane, -10°C	76.3%
	5	4.0	THF/heptane, 20°C	THF/heptane, 5°C	72.1%
	6	4.0	THF/heptane, 20°C	THF/heptane, 20°C	70.4%

Applicants are prepared to present the above information (submitted here in the interest of timely filing) in declaration format if such is deemed necessary.

Based on the foregoing discussion, Applicants submit that each and every element of Claims 1, 5, 15, and 22 (as now present) is not taught or disclosed by Czernecki, therefore there can be no anticipation of any of these claims. Accordingly, this rejection under §102 should be withdrawn and such action is respectfully requested.

The Rejection under 35 U.S.C. §103

Claims 1-4, 6, 9-13, 15-19 and 23-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Czernecki in combination with Hawley's Chemical Dictionary, and Grant & Hackh's Chemical Dictionary. The action states that it would have been obvious to one of ordinary skill in the art to use a non-cryogenic process comprising forming a lithiated anionic species and coupling it with a carbonyl substituted compound to form a glycoside as is instantly claimed, since

the reagents, process steps and conditions are taught in the prior art. Applicants respectfully traverse.

Applicants first note that the invention is not rooted necessarily or wholly in the selection of reagents and the general chemistry that generates the glycoside product. Rather, Applicants' invention as claimed is defined as a continuous process wherein the chemical reactions are conducted in whole at non-cryogenic temperatures by virtue of using a microreactor, and use of both of these non-cryogenic process steps was not contemplated and suggested in the prior art for the preparation of glycosides with this chemistry.

The Examiner maintains that Czernecki teaches the lithiation step as well as the coupling step at low temperatures, namely  $-78^{\circ}\text{C}$  and  $-40^{\circ}\text{C}$ . It is also stated that it is well known in the art to vary process conditions like temperature. However, as pointed out above, these are different from the non-cryogenic conditions specified for both the lithiation step, and the coupling step, of Applicants' invention. Moreover, Czernecki teaches a batch process which does not demonstrate, suggest or even contemplate the unexpected benefit to be gained from conducting the reactions in a microreactor, one of which is the ability to run the process at higher temperatures than the conventional cryogenic temperatures while producing elevated yield and therefore a purer product. The advantages shown by the results of the claimed process are demonstrated, as discussed above, in Table 1.

Czernecki teaches the reaction of carbonyl substituted compound (1) with the lithiated aromatic compound (3a or 3b) to form the glycoside 5 and 8 at cryogenic temperatures. The lithiated aromatic anionic species is prepared by reacting the aromatic compound 2a or 2b (aromatic halide) wherein bromine (a halide) is the leaving group. In response, Applicants point out that the claimed invention comprises performing the chemical reactions responsible for formation of glycoside in a continuous process in at least one microreactor or a series of microreactors, using non-cryogenic temperatures in both the lithiating step and the coupling step.

The action goes on to note that the formation of compound 4 (Table 1) predominates, and that the results should be interpreted to indicate that a very high percentage of the lithiated anionic species is formed which, the Examiner presumes, would automatically translate to a higher amount of the desired glycoside being formed. The Examiner adds that the required species 3 is formed in greater amount at higher temperatures since the corresponding hydrolysis product 4 is obtained in

higher yield. The action also focuses on the use of sec-butyl lithium, arguing that one of ordinary skill in the art knows that n-butyl lithium and t-butyl lithium are both used in lithiation reactions, and relies on the definition of "metalating agent" in Hawley's Dictionary. Applicants disagree. As discussed above, the overall yield to be expected from the Czernecki process could be expected to be relatively low. The 98% yield is not from a cryogenic lithiation and coupling; the overall yield was seen to be on the order of about 62% after execution of the lithiation and cryogenic coupling steps. (See page 6291, right hand column of Czernecki.) The continuous process of the invention using one or more microreactors at non-cryogenic temperatures produces even a higher yield (over 70%) than the cryogenic coupling of Czernecki (62%) which is surprising and unexpected since one skilled in the art would expect a higher yield using cryogenic coupling.

The action also states that Czernecki teaches the use of both THF and toluene in the process; and elsewhere states that Czernecki discloses the use of toluene, petroleum ether and THF. Also in respect of the solvents, the action states that the use of mixtures of aprotic solvents and heptane are obvious variants, and (relying on Grant & Hack's Chemical Dictionary) that heptane is similar to petroleum ether, which is a mixture of pentanes and hexanes. In response, Applicants note that it may indeed be possible to practice the claimed invention with different solvents, thus the cited references are not dispositive on this point either. Rather, it is the combination of the use of a microreactor and carrying out both lithiation and coupling at non-cryogenic temperatures that produces the unexpectedly improved preparation of glycoside product.

Applicants respectfully request that this rejection for obviousness be withdrawn, it having been properly traversed.

#### Conclusion

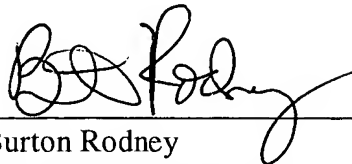
In light of the foregoing amendments and remarks, Applicants submit that all outstanding rejections and observations have been met and overcome, and therefore withdrawal and allowance of the pending claims is requested.

If a direct personal communication might advance the prosecution of this application, the Examiner is invited to contact Applicants' undersigned representative at the telephone number below.

FEE AUTHORIZATION

The Commissioner is authorized to charge any fee required for entry of this amendment, or credit any overpayment thereof to the assignee's Deposit Account No. 19-3880.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Burton Rodney", is written over a horizontal line.

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